REMARKS

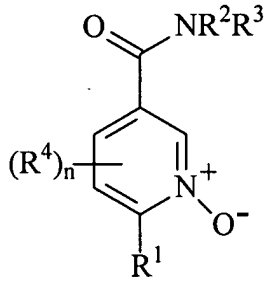
As an initial matter, the Action alleges that Applicants have not amended the claims to the elected group IIIa (wherein R2 is H and R3 is an aryl or an aryl-alkylene). Applicants thank the Examiner for noting this oversight, and respectfully submit that the claims have been amended to recite the elements of elected group IIIa.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 31-42 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. The Action alleges that the ordinary artisan could not make and/or use the instantly claimed invention without undue experimentation.

Applicants respectfully traverse this rejection and submit that the claims are fully supported by the instant specification. As an initial matter, Applicants note that the Action mischaracterizes the claims by stating the compounds cover a wide range, "with R1 being R5 or R5-(C1-C6 heteroalkylene)." *See* p. 2, Office Action dated September 6, 2007. Applicants respectfully submit that the claims do not recite any R5 group, but only recite R1, R2, R3 and R4 groups. Applicants respectfully submit that the claim 31, as amended recites:

A method for antagonizing chemokine receptors comprising administering to a patient in need thereof an effective amount of a compound having the structure (I):



(I)

and optical isomers, diastereomers, enantiomers and pharmaceutically acceptable salts thereof, wherein

R^1 is selected from hydrogen, halogen, alkyl, heteroalkyl, aryl, heteroaryl, carbocycle aliphatic ring and heterocycle aliphatic ring, amino or hydroxy;

R^2 is hydrogen;

R^3 is selected from aryl, aryl(akylene);

each occurrence of R^4 is independently selected from halogen, alkyl, heteroalkyl, aryl, heteroaryl, carbocycle aliphatic ring and amino or hydroxy; and

n is 0 or 1.

Applicants also note that the Action is incorrect in asserting that "There are no examples with the R being heterocyclic groups [sic]...". Applicants respectfully submit that Example 5 sets forth a compound in which R1 is a heterocycle. Thus, this statement is incorrect.

Applicants submit that methods for preparing compounds claimed are disclosed by the teachings of the specification, including the Examples. For instance, claimed compounds wherein R^1 is heteroaryl (particularly, unprotected *N*-heteroaryls) can be prepared in a manner similar to that described in Example 5 (wherein R^1 is imidazol-l-yl). Claimed compounds wherein R^1 is heterocycle aliphatic ring can be prepared in a manner similar to that described in Example 7 (where R^1 is pyrrol-l-yl). Compounds of the invention wherein R^4 is halo, such as those described in Example 15, can be similarly combined with the appropriate *N*-heteroaryl or *N*-heterocycle aliphatic ring under standard conditions to produce compounds of the invention wherein R^4 is heteroaryl. Compounds of the present claims are also described in Examples 1, 16, and 17. Furthermore, Examples 21 and 22 disclose a number of compounds that antagonize chemokine receptors by decreasing binding of the chemokines IL-8 and GRO-α.

Applicants maintain that the Action has failed to establish a *prima facie* case of lack of the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that the *Wands* factors, as set forth herein and as previously made of record, indicate that mere screening assays that are routine practice for the skilled artisan are all that is required to practice the claimed compounds. Applicants

respectfully submit such routine procedures do not rise to the level of experimentation, and as such no undue experimentation is needed to practice the claimed compounds.

Applicants set forth the following *Wands* factor analysis:

1. *Quantity of experimentation necessary.* Applicants submit that the skilled artisan would be readily able to screen the claimed compounds for inhibition of binding of specific chemokine receptors, as taught by the instant specification for example, at pages 47-68. Applicants submit that the Action mischaracterizes Table 6, by incorrectly stating that this table indicates IC50 values. Applicants submit that the Reference Data charts throughout the application as filed indicate IC50 values. However, Table 6 instead refers more generally to a relative higher or lower activity, and not IC50 values, as discussed in more detail herein. Applicants submit that merely because negative results are obtained for binding assays, under *Wands* it is acceptable to claim potentially non-operative embodiments and such embodiments do not discount the claimed invention.

To reiterate arguments previously made of record, the court found in *Wands* that even if a success rate was low, it would not defeat enablement if the experimentation was not undue.

2. *Amount of direction or guidance provided.* Applicants submit that the skilled artisan, with basic knowledge of organic chemistry, would be fully able to practice the claims in light of the teachings of the instant application. Applicants note that the original application as filed at, for example, pages 23-29, as well as the numerous Examples, provide guidance for practicing the instant claims.

As set forth above, Applicants respectfully submit that the application as filed sets forth extensive direction for making and using the present claims. For example, . as indicated in Examples 21 and 22, compounds of the present claims were screened at 20 μM and 10 μM concentrations, respectively. Tables 3-6 set forth compound activity wherein "*" indicates less than 40% receptor inhibition, while "**" indicates greater than 40% receptor inhibition. Thus, Tables 3-6 represent two levels of receptor antagonism in the form of measured receptor inhibition. Applicants reiterate that these tables do not set forth IC50 values, as asserted by the Action, but instead refer to receptor inhibition, with "*" indicating lesser activity, and "**" indicating greater activity.

3. *Presence of working examples.* Applicants note that Examples 1, 16, 17, 21, and 22, as well as Tables 3-6 teach 95 claimed compounds. Applicants submit that these Examples and Tables set forth numerous different species of the claimed genus, as well as information relating to relative activity, as measured by receptor inhibition. Applicants submit that the skilled artisan could readily screen for other compounds, as set forth in the Examples, in light of the teachings of the instant application as filed.

4. *Nature of the invention.* The nature of the instant claims provide for assays described in the specification that are conventional and routinely practiced by the skilled artisan. For example, pages 64-66 of the instant specification provide for such routine screening procedures.

5. *The state of the prior art.* As iterated herein, the court in *Wands* found that the methods needed to practice the invention were well-known, as is similar to the instant claims. While the Action alleges that "there is no absolute predictability and no established correlation between *in vitro* activity and the treatment of various diseases, and also the IC50 values, as the *in vitro* data is not a reliable predictor of success even in view of the seemingly high level of skill in the art." *See* page 3, Office Action dated September 6, 2007. Applicants respectfully submit that "absolute predictability" is not the standard for the enablement requirement under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that if "absolute predictability," were the standard for enablement for pharmaceutical compounds, then very few pharmaceutical compounds would be patentable.

6. *The relative skill of those in the art.* The skill in the art is high, as conceded by the Action.

7. *The predictability or unpredictability of the art.* As an initial matter, Applicant notes that the Action alleges that "the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity," See page 3, of Office Action dated September 6, 2007. Applicants respectfully submit that no basis is provided for this statement, and respectfully submit that, as previously made of record, the determination of enablement is based on the evidence as a whole, and "the examiner should never make the determination based on personal opinion. The

determination should always be based on the weight of all the evidence." See MPEP 2164.05 (emphasis original).

Applicants respectfully submit that if the Examiner is relying on "common knowledge" or "taking official notice," with regard to the statement that "the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity," then the Examiner must provide documentary evidence in the next Office Action if the rejection is to be maintained. See 37 C.F.R. §1.104(c)(2); MPEP 2144.03. Applicants further submit that if the Examiner is relying on personal knowledge to support the finding of what is known in the art, the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 C.F.R. §1.104(d)(2).

Applicants further submit that the skilled artisan, given the teachings of the instant application at the time of filing, as well as the general knowledge and skill level, would be able to mitigate any level of unpredictability in the art of pharmaceutical drug development.

8. *The breadth of the claims.* Applicants submit that the Action has not set forth any substantive rationale that indicate a lack of enablement under 35 U.S.C. § 112, first paragraph. While the Action maintains reference to *Genentech v. NovoNordisk*, as a patent application not being a "hunting license," analogy from *Brenner v. Hanson,* Applicants note that this reference relates to a utility requirement, and thus is inapplicable to the enablement rejection at hand. Applicants submit that the breadth of the claims reflects the breadth of the instant disclosure. As stated herein, Examples 1, 16, 17, 21, and 22, as well as Tables 3-6 teach 95 claimed compounds. Thus, the breadth of the claims is fully supported by numerous species of the claimed genus of compounds.

In view of the foregoing remarks and amendments, Applicants submit that the Action has not met its burden of showing a *prima facie* case of lack of enablement under 35 U.S.C. § 112, first paragraph, or that undue experimentation is required in order to practice the invention as claimed. Accordingly, Applicants respectfully request reconsideration and withdrawl of this rejection.

If additional fees are believed necessary, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

All of the claims in the application are believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 757-8122.

Respectfully submitted,
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